REMARKS

Claims 56-61, 64-68, 84-93, and 96-103 are currently pending in the application.

35 U.S.C. §103(a) - Previous rejections

The previous rejections of claims 56-61, 64-68, 84-93, and 96-100 under 35 U.S.C. §103(a) based on Chee et al. (U.S. 2003/01808867; Chee) in view of Kain et al. (US 2002/0039728; Kain) have been withdrawn (Office Action, page 2).

35 U.S.C. §103(a) - Objective evidence of nonobviousness

Applicants respectfully request reconsideration of the objective evidence for nonobviousness presented in the Amendment and Response filed October 14, 2005 for at least the reasons that: 1) the Office failed to consider and address the evidence for the unexpected results and long-felt need for the claimed invention; 2) the Office failed to properly evaluate the objective evidence as rebuttal to an alleged *prima facie* case; and 3) the Office failed to evaluate the nexus of the objective evidence to the claimed invention.

Applicants set forth these matters as follows.

Office requirement to fully consider and address Applicants' arguments

In the Amendment and Response filed October 14, 2005, Applicants submitted objective evidence for nonobviousness of the present invention, including proof of 1) unexpected results; 2) long-felt need; and 3) commercial success. In the Office Action mailed December 29, 2005, the Office considered only the evidence for commercial success for the invention, and failed to consider and address the evidence for the unexpected results and long-felt need for the claimed invention as shown in the *Nature* and *The New York Times* articles and the 454 and Roche Press Releases.

The *Nature* article describes Applicants' sequencing substrate and apparatus as providing a system for "whole-genome sequencing" (Exhibit 1, page 1, left column, submitted previously). The article notes that the system is capable of generating 47 million bases of sequence information from test fragments (Exhibit 1, page 4, left column, submitted previously). The article points out that the system can be used at 100% accuracy over greater than 400 bases on single reads (Exhibit 1, page 4, right column, submitted previously). The article states that typical runs can be used to generate 25 million bases of sequence information at an estimated accuracy of 99% or higher (Exhibit 1, page 1, right column, submitted previously). The article notes that Sanger sequencing is substantially slower, less efficient, and more expensive (Exhibit 1, page 1, left column and page 4, right column, submitted previously). The *Nature* article emphasizes the need to replace the Sanger method (developed in 1981) for large-scale sequencing (Exhibit 1, page 1, left column, submitted previously).

The *New York Times* article recognizes Applicants' sequencing substrate and apparatus as making "giant strides towards the goal of sequencing the human genome so cheaply that it could be done routinely for medical reasons" (Exhibit 2, page 1, submitted previously). The article makes specific reference to Applicants' use of beads attached with DNA, luciferase, and the "light-sensitive chip" which is distinguished from other sequencing approaches (Exhibit 2, page 2, submitted previously). In the article, Dr. Rothberg (Chairman of 454 Life Sciences and inventor for the instant application) points to the exclusive ability of the system to sequence novel genomes and to re-sequence the human genome at a cost of $1 million (Exhibit 2, page 2, submitted previously). The *Times* article notes that the Human Genome Project completed in 2003 cost approximately $800 million (Exhibit 2, page 2, submitted previously).

The 454 Press Release specifically notes Applicants' "novel instrumentation...[for] high-throughput nucleotide sequencing, with specific application to sequencing of whole genomes" (Exhibit 3, paragraph 4, submitted previously). The 454 Press Release notes that the instrument is capable of producing more than 20 million bases per run, which is 100 times the capacity of other sequencing systems (Exhibit 3, paragraph 5, submitted previously). The Roche Press

Release also confirms the systems' ability to produce more than 20 million bases in each sequencing run (Exhibit 4, paragraph 3, submitted previously). The Roche Press Release states that Applicants' sequencing substrate and apparatus provide a "scalable, ultra-fast, and cost-effective system with applications for whole genome sequencing" (Exhibit 4, paragraph 3, submitted previously). The Roche press release notes that "Customer feedback and our own research show that one of the main limitations of today's approaches to sequencing is throughput. This new technology will significantly increase the speed of sequencing, and thereby has the potential to open up many new applications...all over the world" (Exhibit 4, paragraph 4, submitted previously).

Applicants note that the *Nature* and *Times* articles emphasize the long felt need to replace Sanger sequencing, and fail to mention Chee or Kain (or Krull) as alternatives. *See Graham v. John Deere*, 383 U.S. 1, 17-18 (1966). By comparison, the claimed substrate and apparatus have been recognized as producing sequencing arrays which far surpass the Sanger substrates. The unexpected results and long-felt need for Applicants' devices have been recognized by top-tier publications (and editors and reviewers). Few inventions receive this level of public and peer acknowledgment. As such, this is compelling evidence for the non-obviousness of Applicants' claims.

The Manual for Patent Examining Procedure states that the Examiner should consider the traversals presented by Applicants and answer the substance of each argument. MPEP §707.07(f). The importance of answering Applicants' arguments is recognized by the Office for providing a complete file history and clear prosecution record. *Id.* Applicants respectfully request evaluation of all arguments presented herein and in the Amendment and Response filed October 14, 2005.

Objective evidence to rebut alleged *prima facie* case

In the Office Action mailed December 29, 2005, the Office failed to properly evaluate the objective evidence of nonobviousness, including the unexpected results, long-felt need, and

commercial success of the claimed invention. The Examiner dismissed the commercial evidence of nonobviousness by arguing that the Chee device is physically similar to the claimed wafer when coupled to an additional optic fiber (Office Action, page 9). By this, the Examiner has merely restated the alleged basis for a *prima facie* case of obviousness (i.e., supposed similarities to Chee) and has disregarded the evidence showing unexpected results and long-felt need for the invention. Applicants traverse this for reasons of record, and submit that the Examiner's argument is insufficient for negating any of the submitted evidence for nonobviousness.

Objective evidence can be presented to rebut an alleged *prima facie* case of obviousness. MPEP §2144.08(II)(B). This means that, *even if every element of the claimed invention is taught or suggested in the cited references* (i.e., a *prima facie* case is made), the claimed invention *can still be considered nonobvious* with sufficient showing of unexpected results, long-felt need, commercial success, or other objective evidence. *Id.* Thus, the alleged similarities shown by Chee (or Krull) to the present invention *cannot* be used to refute the objective evidence of nonobviousness presented herein and in the Amendment and Response filed October 14, 2005. Rather, the objective evidence must be considered apart from any *prima facie* findings. MPEP §2144.08(II)(B).

Applicants point to the recent Federal Circuit decision in *Kao Corporation v. Unilever United States*, which has held:

> Unilever argues that even if we accept Kao's evidence of unexpected results, the remaining evidence in the record is so overwhelming that the unexpected results are insufficient to overcome it. It argues that the two prior art references "disclose every limitation of the claimed invention and provide a strong motivation for their combination," ...*Unilever's argument is not sustainable. The "overwhelming evidence" it cites is little more than the very evidence used to establish the* prima facie *case. If the evidence used to establish the* prima facie *case were necessarily sufficient to overcome rebuttal of that case, rebuttal would be impossible. That result is simply not logical*.

-- and --

> *Certainly we have stated on several occasions that unexpected results may be sufficient to rebut a* prima facie *case of obviousness*. *See, e.g., In re De Blauwe*, 736 F.2d 699, 706 n. 8 (Fed. Cir. 1984) (stating that "[a] proper showing of unexpected results will rebut a prima facie case of obviousness"). *Kao Corporation v. Unilever United States*, 441 F.3d 963, 970 (Fed. Cir. 2006).

Here and in the Amendment and Response filed October 14, 2005, Applicants have presented proof of the unexpected results and long-felt need for Applicants' device as recognized in the top-tier scientific publication of *Nature* and the top-tier news publication of the *New York Times*. Applicants have previously presented proof of the commercial success of Applicants' device as shown in the world-wide licensing agreement made with Roche Diagnostics for $62 million. This objective evidence must be considered as proof of nonobviousness of the claimed invention and cannot be dismissed by merely restating supposed similarities to Chee and/or Krull.

The Examiner states that portability of the claimed substrate is not sufficient by itself for patentability " '*unless there are new or unexpected results*' " (Office Action, page 6 (emphasis in original), citing *In re Lindberg*). The Examiner states that "no new or unexpected results are produced" by the claimed substrate (Office Action, page 7). However, the Examiner has failed to consider or address the unexpected results presented by Applicants herein and in the and Response filed October 14, 2005. The *Nature* paper, in particular, notes the new and unexpected results of Applicants' invention including:

- Production of 47 million bases of sequence information from test fragments;
- Production of 25 million bases of sequence information at an estimated accuracy of 99% or higher; and
- Capability for 100% accuracy over greater than 400 bases on single reads;

- Sequencing at substantially faster, more efficient, and cheaper rates than Sanger methods (see above).

The surprising features of Applicants' invention (e.g., massively parallel capacity, efficiency, and greatly reduced costs) are further recognized by *The New York Times* and the 454 and Roche press releases.

Regarding unexpected results, the *New York Times* article recognizes Applicants' sequencing substrate and apparatus as making "giant strides towards the goal of sequencing the human genome so cheaply that it could be done routinely for medical reasons" (Exhibit 2, page 1, submitted previously). The 454 Press Release specifically notes Applicants' "novel instrumentation...[for] high-throughput nucleotide sequencing, with specific application to sequencing of whole genomes" (Exhibit 3, paragraph 4, submitted previously). The 454 Press Release notes that the instrument is capable of producing more than 20 million bases per run, which is 100 times the capacity of other sequencing systems (Exhibit 3, paragraph 5, submitted previously). The Roche Press Release also confirms the systems' ability to produce more than 20 million bases in each sequencing run (Exhibit 4, paragraph 3, submitted previously). This is further corroborated by the system description from Roche Applied Sciences, which also notes the *Nature* article (Exhibit 5, page 1, submitted previously). The Roche Press Release states that Applicants' sequencing substrate and apparatus provide a "scalable, ultra-fast, and cost-effective system with applications for whole genome sequencing" (Exhibit 4, paragraph 3, submitted previously).

Regarding long-felt need, the *Nature* article notes that Sanger sequencing is substantially slower, less efficient, and more expensive than Applicants sequencing substrate and apparatus (Exhibit 1, page 1, left column and page 4, right column, submitted previously). The *Nature* article emphasizes the need to replace the Sanger method (developed in 1981) for large-scale sequencing (Exhibit 1, page 1, left column, submitted previously). The *Times* article points to the exclusive ability of the system to sequence novel genomes and to re-sequence the human

genome at a cost of $1 million (Exhibit 2, page 2, submitted previously). The *Times* article notes that the Human Genome Project completed in 2003 cost approximately $800 million (Exhibit 2, page 2, submitted previously). The Roche press release notes that "Customer feedback and our own research show that one of the main limitations of today's approaches to sequencing is throughput. This new technology will significantly increase the speed of sequencing, and thereby has the potential to open up many new applications...all over the world" (Exhibit 4, paragraph 4, submitted previously).

Regarding commercial success, the 454 Press Release indicates that Applicants' sequencing substrate and apparatus have been licensed by Roche Diagnostics in a $62 million world-wide agreement for promotion, sale, and distribution of 454's Genome Sequencing Systems (Exhibit 3, paragraph 3, submitted previously). The Press Release notes that 454 Life Sciences has already received $11.5 million from Roche Diagnostics in milestones for the commercial release of the Genome Sequencing Systems and reagents (Exhibit 3, paragraphs 1 and 3, submitted previously). The Roche Press release confirms the $62 million licensing agreement with 454 Life Sciences for the promotion, sale, and distribution of 454's Genome Sequencing Systems (Exhibit 4, paragraphs 2 and 5, submitted previously).

As further evidence of unexpected results, long-felt need, and commercial success, Applicants submit herewith a NewsRx™ article indicating that the U.S. National Center for Biotechnology Information ("NCBI") has added a new sequence submission format to accept data from Applicants' invention (Exhibit A, attached, "U.S. biotechnology information center adds new standard submission format for its Trace Archive," February 27, 2006; see also, Exhibit B, attached, "NCBI adopts standard for accepting 454 Life Sciences' Sequencing Data," January 27, 2006). The new NCBI submission format allows data generated with Applicants' sequencing substrate and apparatus to be directly entered into NCBI trace sequence archives (Exhibit A, paragraph 2). This represents the first new format to be adopted by the NCBI since the Sanger sequencing method originally developed in 1977 (Exhibit A, paragraph 2). Since inception in late February, 2006, at least 6,264,298 traces (i.e., nucleotide sequences) have been archived in the NCBI database using Applicants' sequencing invention (Exhibit C, attached,

http://www.ncbi.nlm.nih.gov/Traces/trace.cgi?). This includes the landmark sequence information for *Mammuthus primigenius* (wooly mammoth) published by Dr. Stephan C. Schuster (Exhibit A, paragraph 3; Exhibit B, paragraph 2).

The NCBI is a division of the National Library of Medicine at the National Institutes of Health (Exhibit A, paragraph 5). The NCBI is a world leader in the organization and analysis of sequence information. The NCBI regulates the GenBank sequence database and maintains data exchange with the international nucleotide sequence databases, European Molecular Biology Laboratory (EMBL) and the DNA Database of Japan (DDBJ). The NCBI incorporates patented sequence data from the U.S. Patent and Trademark Office. The NCBI supports and distributes a variety of medical databases, including the Online Mendelian Inheritance in Man (OMIM), the Molecular Modeling Database (MMDB) of 3D protein structures, the Unique Human Gene Sequence Collection (UniGene), a Gene Map of the Human Genome, the Taxonomy Browser, and the Cancer Genome Anatomy Project (CGAP), in collaboration with the National Cancer Institute. The NCBI provides BLAST tools that are instrumental in sequence similarity searching and in the identification of genes and genetic features. The NCBI provides Entrez search and retrieval systems with integrated access to sequence, mapping, taxonomy, and structural data. The NCBI provides PubMed, a Web search interface that provides access to over 11 million journal citations in MEDLINE and contains links to full-text articles at participating publishers' Web sites.

The NCBI's recognition and adoption of a new sequence submission format from Applicants' invention is clear evidence of unexpected results (i.e., superior functioning). The unexpected results, long-felt need, and commercial success of Applicants' invention is further evident in the entry of over 6.2 million traces (i.e., nucleotide sequences) in only 3 months since inception of the new sequence submission format by NCBI (Exhibit C, attached, http://www.ncbi.nlm.nih.gov/Traces/trace.cgi?). The commercial success shown by the submitted evidence is derived from claimed features and inherent advantages of the invention, and is not the result of heavy promotion or advertising, shift in advertising, consumption by

purchasers normally tied to applicant or assignee, or other extraneous business events. MPEP §716.03(b). The surprising features of Applicants' invention (e.g., massively parallel capacity, efficiency, and greatly reduced costs) are also recognized by *Nature*, *The New York Times*, and the 454 and Roche press releases submitted previously (see above). Applicants conclude that the totality of this evidence provides considerable proof that the claimed invention could not be considered obvious in view of *any* cited publications.

The Examiner has dismissed the objective evidence provided by Applicants without full consideration of the proofs presented. The Examiner argues that the Chee device is physically similar to the claimed wafer when coupled to an additional optic fiber (Office Action, page 9), and merely restates the alleged basis for a *prima facie* case of obviousness (i.e., supposed similarities to Chee). Applicants again assert that the Examiner has failed to answer the substance of *all* of the objective evidence presented (MPEP §707.07(f)), and that Examiner's argument is *insufficient* for negating the provided evidence for nonobviousness (MPEP §2144.08(II)(B)). The Federal Circuit has stated "If the evidence used to establish the *prima facie* case were necessarily sufficient to overcome rebuttal of that case, rebuttal would be impossible. That result is simply not logical... [W]e have stated on several occasions that unexpected results may be sufficient to rebut a *prima facie* case of obviousness." *Kao Corporation*, 441 F.3d at 970.

Under the legal standard for §103, even if Chee and Krull *could* be combined to teach or suggest each and every element of the invention (which is still disputed), the highly unexpected and improved results for the claimed substrate and apparatus are sufficient to establish nonobviousness. *See In re Albrecht*, 514 F.2d 1389, 1396 (C.C.P.A. 1975); MPEP §2144.08. Any supposed similarities to Chee or Krull *cannot* be used to refute the objective evidence; the evidence must be considered under new analysis, apart from any *prima facie* findings. MPEP §2144.08(II)(B); *Kao Corporation*, 441 F.3d at 970. Applicants respectfully request proper consideration of the objective indicia, including the unexpected results, long-felt need, and commercial success for the claimed invention.

Nexus of objective evidence to the claimed invention

In the Office Action mailed December 29, 2005, the Office failed to properly evaluate the nexus of the objective evidence for nonobviousness to the claimed invention. The Examiner dismissed the objective evidence by arguing that the commercial success of the invention shows an insufficient nexus to the claimed features that are distinguished from Chee (Office Action, page 9). By this, the Examiner has misstated the nexus requirement and set aside the objective evidence based on supposed similarities to Chee (i.e., the alleged *prima facie* findings). Applicants submit that the Examiner's arguments are insufficient for negating the objective evidence for nonobviousness or its nexus to the claims.

As noted above, objective evidence for nonobviousness can be presented to rebut an alleged *prima facie* case. MPEP §2144.08(II)(B). This means that, *even if every element of the claimed invention is taught or suggested in the cited references* (i.e., a *prima facie* case is made), the claimed invention *can still be considered nonobvious* with sufficient showing of unexpected results, long-felt need, commercial success, or other objective evidence. *Id.* Thus, the alleged similarities shown by Chee (or Krull) to the present invention *cannot* be used to refute the objective evidence of nonobviousness (or its nexus) presented herein and in the Amendment and Response filed October 14, 2005. *Kao Corporation*, 441 F.3d at 970. Rather, the objective evidence must be considered apart from any *prima facie* findings. MPEP §2144.08(II)(B).

Under §103, the nexus requirement states that the objective evidence must have a reasonable factual and legal connection to the claimed invention so that the evidence is of probative value in the determination of nonobviousness. MPEP §716.01(b) and §2144.08(II)(B). Yet, only a reasonable correlation is required, and unexpected results and commercial success need not be presented over the entire range of the claims. *See* MPEP §716.01(b); §716.03(a)(II); and §2144.08(II)(B) It is sufficient to show unexpected properties for an exemplary embodiment of the invention. *See, e.g., In re Chupp*, 816 F.2d 643, 646 (Fed. Cir. 1987); MPEP

§2144.08(II)(B). Thus, an exemplary showing may be sufficient to establish a reasonable correlation between the objective evidence and the scope of the claim. *Id.*

Here and in the Amendment and Response filed October 14, 2005, Applicants have demonstrated a sufficient nexus for the objective evidence to the claimed invention.

Applicants point to the evidence of the *Nature* article, which shows a reasonable correlation with the claims, including:

- A fiber optic slide etched to produced 1.6 million wells (Exhibit 1, page 2, left column, submitted previously[1]);
- with a fiber diameter of 47 μm (Exhibit 1, page 2, left column, submitted previously[2]);
- with a well depth of 55 μm (Exhibit 1, page 2, left column, submitted previously[3]);
- with beads attached with genomic DNA (Exhibit 1, Figure 1, submitted previously[4]);
- with beads attached with sulfurylase and luciferase as sequencing enzymes (Exhibit 1, page 5, left column, submitted previously[5]);
- with a flow chamber for holding the fiber optic slide (Exhibit 1, page 2, Figure 2, submitted previously[6]);
- with a fluidic assembly for delivering individual nucleotides (Exhibit 1, page 2, Figure 2, submitted previously[7]); and

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[1] See instant **claims 56 and 84**: cavitated fiber optic wafer...at least 10,000 wells...etched into the top surface; and **claim 66**: *wherein said substrate comprises 10^5 or more different groups of nucleic acid sequences in discrete regions.*

[2] See instant **claims 56 and 84**: *each individual optical fiber having a diameter between 3 and 100 μm*; and **claim 85**: *wherein the diameter of each individual optic fiber in the cavitated wafer is between 6-50 μm.*

[3] See instant **claims 56 and 84**: *the depth of each well ranges from between one half the diameter of an individual optical fiber and three times the diameter of an individual optical fiber.*

[4] See instant **claims 57 and 100**: *wherein the nucleic acid is immobilized on the wells or on said beads*; and **claim 87**: *wherein the nucleic acid is DNA.*

[5] See instant **claims 56 and 84**: *said beads having a pyrophosphate sequencing reagent attached thereto*; and **claims 92 and 93**: *wherein said pyrophosphate sequencing reagent is luciferase [sulfurylase].*

[6] See instant **claim 84**: *a flow chamber having disposed therein a cavitated fiber optic wafer.*

[7] See instant **claim 84**: *fluid means for delivering additional pyrophosphate sequencing reagents, including sequential delivery of nucleotide triphosphates.*

- with CCD camera-based image capture (Exhibit 1, page 5, left column, submitted previously[8]).

Applicants point to the evidence of the *Times* article, which shows a reasonable correlation with the claims, including:

- a "light-sensitive chip" (Exhibit 2, page 2, submitted previously[9]);
- with beads attached with genomic DNA (Exhibit 2, page 2, submitted previously[10]); and
- luciferase (Exhibit 2, page 2, submitted previously[11]).

Applicants point to the system description from Roche Applied Sciences (Exhibit 5, page 1, submitted previously; "Reference: www.nature.com"), which connects to the *Nature* paper and thereby shows a reasonable correlation with the claims, including:

- A fiber optic slide etched to produced 1.6 million wells;
- with a fiber diameter of 47 μm;
- with a well depth of 55 μm;
- with beads attached with genomic DNA;
- with beads attached with sulfurylase and luciferase as sequencing enzymes;
- with a flow chamber for holding the fiber optic slide;
- with a fluidic assembly for delivering individual nucleotides; and
- with CCD camera-based image capture (see above).

[8] See instant **claim 84**: *detection means for detecting optical signals from each well*; and **claim 86**: *wherein said detection means is a CCD camera.*
[9] See instant **claims 56 and 84**: *cavitated fiber optic wafer...*
[10] See instant **claims 57 and 100**: *wherein the nucleic acid is immobilized on the wells or on said beads*; and **claim 87**: *wherein the nucleic acid is DNA.*
[11] See instant **claims 56 and 84**: *said beads having a pyrophosphate sequencing reagent attached thereto*; and **claims 92 and 93**: *wherein said pyrophosphate sequencing reagent is luciferase.*

Applicants point to the press release regarding the new NCBI sequence format (Exhibit B, page 3; "Published Proof: Our Nature Paper"), which connects to the *Nature* paper and thereby shows a reasonable correlation with the claims, including:

- A fiber optic slide etched to produced 1.6 million wells;
- with a fiber diameter of 47 μm;
- with a well depth of 55 μm;
- with beads attached with genomic DNA;
- with beads attached with sulfurylase and luciferase as sequencing enzymes;
- with a flow chamber for holding the fiber optic slide;
- with a fluidic assembly for delivering individual nucleotides; and
- with CCD camera-based image capture (see above).

Thus, the objective evidence presented to the Patent Office shows a reasonable factual and legal connection to the claimed invention so that the evidence is of probative value in the determination of nonobviousness. *See* MPEP §716.01(b) and §2144.08(II)(B). Applicants have shown a reasonable correlation to the claims, as unexpected results and commercial success need not be presented over the entire range of the claims. *See* MPEP §716.01(b); §716.03(a)(II); and §2144.08(II)(B) Here, it is sufficient to show unexpected properties for an exemplary embodiment (e.g., specific size range) of the invention. *See, e.g., Chupp*, 816 F.2d at 646; MPEP §2144.08(II)(B). The exemplary embodiment can be considered sufficient to establish a nexus between the evidence and the scope of the claims. *Id.*

As such, the unexpected results, long-felt need, and commercial success presented by Applicants show a sufficient nexus to the claimed invention. In the Office Action, the Examiner misstates the nexus requirement, and fails to properly consider the objective evidence for nonobviousness presented in the application. The supposed similarities to Chee (i.e., alleged basis for a *prima facie* case) *cannot* be used to refute the objective evidence (or its nexus) to the claimed invention. *See Kao Corporation*, 441 F.3d at 970. The objective evidence must be

considered under new analysis, separate from *prima facie* findings. MPEP §2144.08(II)(B). Applicants respectfully request proper evaluation of the objective indicia, including unexpected results, long-felt need, and commercial success for the claimed invention.

Reconsideration is respectfully requested.

35 U.S.C. §103(a) - *Krull* reference

Claims 56-61, 64-68, 84-93, and 96-103 have been newly rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Chee et al. (U.S. 2003/01808867; Chee) in view of Krull et al. (WO 98/58079; Krull) (Office Action, page 3). The Examiner states that Chee does not disclose the use of a cavitated fiber optic bundle as a wafer with a depth between 0.5 mm and 5.0 mm (Office Action, page 4). However, the Examiner states that Krull discloses the use of an "optical wafer" or "optical fiber." *Id.* Based on this, the Examiner concludes that it would have been obvious for one of skill in the art to combine the teachings of Chee with Krull to obtain the claimed invention.

Applicants respectfully traverse this rejection for at least the bases that: 1) Chee and Krull do not teach or suggest all of the elements of the instant claims; 2) there is no suggestion or motivation to modify Chee with Krull to obtain the claimed invention; and 3) Krull leads away from the invention as claimed. Moreover, it is again asserted that, *even if a prima facie case of obviousness is established* (which Applicants dispute), the claimed invention *is still considered nonobvious* in view of the substantial objective evidence of unexpected results, long-felt need, commercial success of the invention as indicated here and in the Amendment and Response filed October 14, 2005. *See Kao Corporation*, 441 F.3d at 970.

Chee and *Krull* do not teach or suggest all of the claimed elements

For analysis under 35 U.S.C. §103, it is essential to consider all of the elements of the claimed invention. It is impermissible to compare the cited references with what the viewer

interprets as the "gist" of the invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1548 (Fed. Cir. 1983); *Jones v. Hardy*, 727 F.2d 1524, 1530 (Fed. Cir. 1984); and MPEP §2141.02. Each express claim limitation must be taken into account. *See, e.g., Bausch & Lomb v. Barnes-Hind/Hydrocurve, Inc.*, 796 F.2d 443, 447-49 (Fed. Cir. 1986); MPEP §2141.02.

Here, the claims encompass a *cavitated fiber optic wafer*, where the thickness of the wafer (i.e., length of the optic fiber) between the top surface and the bottom surface is *between 0.5 mm and 5.0 mm.*

Regarding the length of the optic fibers, Chee relies on WO 98/50782 (see Chee ¶ [0007]), which reports the use of fibers that are several meters long. As cited by the Examiner, Krull reports the use of *long optic fibers* (see Krull, Figs. 4A-4C; Fig. 5; and Figs. 7A-7C) or *flat, non-fiber wafers* (see Krull, Fig. 21). Neither Chee nor Krull teach or suggest the use of a cavitated fiber optic wafer between 0.5 mm and 5.0 mm in thickness.

When read in context, the "optical wafer" reported by Krull, is actually a flat silica or silicon wafer which contains no optical fibers or cavities (see Krull, page 76, lines 15-20). The smooth aspects of the wafer are critical to the sensor reported by Krull (see above). Krull specifically distinguishes between flat wafers and optical fibers as disparate optical substrates (see Krull, page 32, lines 22-29). For optic fibers, Krull reports that longer is better (see Krull, page 38, lines 26-28). At no point does Krull teach or suggest the use of a *cavitated fiber optic wafer.*

The "optical wafer" from Krull has been presented to show the "gist" of Applicants' invention, while disregarding the specifically claimed aspects of the cavitated fiber optic wafer with a thickness between 0.5 mm and 5.0 mm. *See Vas-Cath Inc. v. Mahurkar*, 935 F.2d at 1565; *Jones v. Hardy*, 727 F.2d at 1530; MPEP §2141.02. Neither Chee nor Krull teach or suggest the use of a cavitated fiber optic wafer with all of the elements claimed herein.

As additional support for this argument, Applicants note that Chee does not teach the "delivery" of a solution comprising a pyrophosphate sequencing reagent (encompassed by instant claims 84-87 and 96-100); nor is this teaching provided by Krull. Applicants also note that neither Chee nor Krull teach or suggest the use of wells with depths ranging from between one half the diameter of an individual optical fiber and three times the diameter of an individual optical fiber (encompassed by instant claims 56-61, 64-68, 84-93, and 96-100). As such, the combination of Chee with Krull cannot make obvious the subject matter of the present claims.

There is no suggestion to modify *Chee* with *Krull* to obtain the claimed invention

Under §103, the fact that the claimed invention is alleged to be within the capabilities of one of ordinary skill in the art is not sufficient by itself to establish a *prima facie* case for obviousness. *In re Kotzab*, 217 F.3d 1365, 1371 (Fed. Cir. 2000); MPEP §2143.01. Thus, "although a prior art device may be capable of being modified to run the way the apparatus is claimed, there must be a suggestion or motivation in the reference to do so" in order to establish obviousness. *In re Mills*, 916 F.2d 680, 682 (Fed. Cir. 1990); MPEP §2143.01.

Here, the Examiner states that forming a "wafer" is an obvious modification of the fiber optic cable from Chee, since Krull reports the use of an "optical wafer" (Office Action, page 7). However, as noted above, Krull reports the use of a long optic fiber or a flat, non-fiber wafer. Krull states that optical fibers and flat wafers are distinctly different optical substrates, and that longer optical fibers are preferred. Thus, the combination of Chee and Krull *cannot* be used to obtain a *cavitated fiber optic wafer* as specifically claimed. To distill the instant claims into the "gist" of an optic wafer is improper (see above).

Moreover, the Examiner provides no explanation as to *why* an artisan would want to modify the substrate of Chee to obtain the specifically claimed cavitated fiber optic wafer with a thickness between 0.5 mm and 5.0 mm. No specific suggestion or motivation to combine the references has been stated. Clearly, the Chee authors themselves did not recognize the

advantages of a cavitated fiber optic wafer even though Krull was published almost two years prior to Chee's filing date.

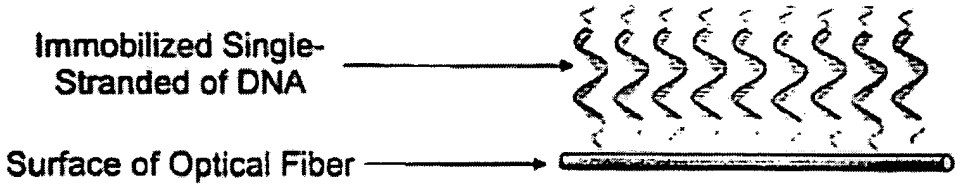
The mere fact that Chee and Krull can be combined in an Office Action is insufficient for establishing obviousness. *See Mills*, 916 F.2d at 682; MPEP §2143.01. The Examiner has provided no evidence of any suggestion or reason for making the combination. As such, the cited references are considered as merely inviting unguided and speculative experimentation, which is not the standard under §103. *In re Jones*, 958 F.2d 347, 350-351 (Fed. Cir. 1992); MPEP §2143.01. Thus, Chee and Krull cannot make obvious the subject matter of the present claims.

Krull leads away from the claimed invention

For rejection under 35 U.S.C. §103, a cited reference must be considered in its entirety, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1552 (Fed. Cir. 1983); MPEP §2141.03. Thus, the Office cannot pick and choose among isolated aspects of the reference, but must consider each reference as a whole. *In re Fitch*, 972 F.2d 1260, 1266 (Fed. Cir. 1992); *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988).

The instant claims encompass a substrate and apparatus comprising a *cavitated fiber optic wafer* with *a plurality of wells* on the top having a nucleic acid therein; and *a plurality of beads* within wells on the top surface of the cavitated wafer of the wafer.

In contrast to the claimed invention, Krull reports the use of a long optic fiber with oligonucleotides uniformly coated on the *longitudinal surface* (not the tip) of the fiber (see Krull, Figs. 4A-4C; Fig. 5; Figs. 7A-7C; and page 21, lines 23-26; Fig. 7B reproduced, in part, below).



For these optic fibers, Krull reports that *increased length of the fiber* provides enhanced function (see Krull, page 38, lines 26-28). As an alternative method, Krull reports the use of a flat, *non-fiber* wafer with oligonucleotides deposited in a continuous layer on the top surface of the wafer (see Krull Fig. 21; page 21, lines 23-26; page 76, lines 15-20; and page 77, lines 23-26).

One key aspect of the Krull sensor is the reported use of a thick, uniform oligonucleotide layer with a greater or equal refractive index than the core of the flat wafer or optic fiber (see Krull, page 10, lines 24-28; page 15, lines 1-8; and page 85, lines 12-27). Krull's oligonucleotide layer forms a film or shell which directs fluorescent light away from the shell and towards a light monitor (see Krull, page 21, lines 23-29).

Importantly, Krull considers this thick, uniform oligonucleotide layer to be a major advancement over the thin films used in previous sensors (see Krull, page 9, lines 29-31 to page 10, lines 1-6; page 21, lines 26-29; and page 34, lines 24-28 to page 35, lines 1-18). Krull notes that imperfections (e.g., roughness) at the oligonucleotide/silica interface can scatter the fluorescent signal, cause leakage of light, and decrease light detection (see Krull, page 74, lines 18-25). Krull also notes the importance of avoiding occlusion on the surface of the flat wafer/fiber optic (see Krull, page 44, lines 21-24).

Krull thereby runs counter to the claimed invention:

- First, Krull indicates that *longer optic fibers are better than shorter ones*. This contradicts the use of a *fiber optic wafer* (see Krull, page 38, lines 26-28);
- Second, Krull's sensor works only with an *oligonucleotide layer applied as a thick, uniform, flat, shell*. This contradicts the use of *nucleic acids in individual wells* (see Krull, page 9, lines 29-31 to page 10, lines 1-6; page 21, lines 26-29; and page 34, lines 24-28 to page 35, lines 1-18);
- Third, Krull's sensor seeks to *avoid surface imperfections and occlusions*. This contradicts the use of *wells and beads* (see Krull, page 74, lines 18-25; and page 44, lines 21-24).

Thus, the Krull sensor would be unsuitable for its intended purpose if produced with nucleic acids in *individual wells* (i.e., discontinuous deposition), *cavitations* of at least 10,000 wells (i.e., numerous surface imperfections) and *beads* on the surface of the wafer (i.e., occlusions of the surface). *See In re Gordon*, 733 F.2d 900, 902 (Fed. Cir. 1984); MPEP §2143.01.

It can be deduced from Krull that i) discontinuous deposition of oligonucleotides would allow fluorescent light to leak back across the oligonucleotide layer and out of the silica substrate (see Krull, page 9, lines 29-31 to page 10, lines 1-6; and page 34, lines 24-28 to page 35, lines 1-18); ii) multiple cavitations would scatter the light signal, cause leakage of light, and decrease light detection (see Krull, page 74, lines 18-25); and iii) beads on the surface of the substrate would occlude the surface and reduce light intensity (see, Krull, page 44, lines 21-23).

Thus, Krull leads away from Applicants' claims. The "optical wafer" reported by Krull has been cited against the instant case without considering the numerous inconsistencies with the claimed invention. Because Krull leads away from the instant claims, Krull cannot properly be combined with Chee for this rejection. MPEP §2146. For this reason and those indicated above, Chee and Krull cannot make obvious the subject matter of the present claims.

Reconsideration is respectfully requested.

35 U.S.C. §103(a) - The legal standard for obviousness

Thus, Chee and Krull cannot make obvious the subject matter of the instant claims for at least the reasons that: 1) Chee and Krull do not teach or suggest all of the elements of the instant claims; 2) there is no suggestion or motivation to modify Chee with Krull to obtain the claimed invention; and 3) Krull leads away from the invention as claimed. Moreover, *even if a prima facie case of obviousness is established based on Chee and Krull* (which remains disputed), the claimed invention *is still considered nonobvious* in view of the substantial showing of unexpected results, long-felt need, commercial success of the invention as demonstrated in this Amendment and in the Amendment and Response filed October 14, 2005.

As evidence of long felt need and unexpected results (i.e., superior function, massively parallel capacity, increased efficiency, and greatly reduced costs), Applicants have submitted proofs of NCBI's recognition and adoption of a new sequence submission format based on the present invention and proofs of recognition by *Nature* and *The New York Times* (see above). As evidence of long felt need, unexpected results, and commercial success, Applicants have submitted proofs of the world-wide, multimillion dollar agreement entered by 454 Life Sciences and Roche Diagnostics and the entry of over 6.2 million traces (i.e., nucleotide sequences) in only 3 months since inception of the new 454 sequence submission format at NCBI (Exhibit C, attached, http://www.ncbi.nlm.nih.gov/Traces/trace.cgi?). In addition, Applicants have demonstrated that the evidence of unexpected results, long-felt need, and commercial success shares a sufficient nexus with the claimed invention.

The totality of the submitted evidence clearly shows that the claimed invention could not be considered obvious in view of *any* cited publications. Any supposed similarities to Chee or Krull (i.e., the supposed *prima facie* case) cannot be used to refute these objective proofs. *Kao*

Corporation, 441 F.3d at 970. The Federal Circuit has stated that arguments such as those presented by the Examiner are improper and lead to an illogical result. *Kao Corporation*, 441 F.3d at 970. Even if Chee and Krull could be combined to teach or suggest all the elements of the instant claims (which is still argued), the surprising and acclaimed results for the claimed invention are sufficient to establish non-obviousness. *See In re Albrecht*, 514 F.2d 1389, 1396 (C.C.P.A. 1975); MPEP §2144.08. Applicants respectfully request proper consideration of the objective evidence, including the unexpected results, long-felt need, and commercial success for the claimed invention.

Regarding Chee and Krull, it is noted that the description in Chee was published on **December 29, 1999** as WO 99/67641.[12] The description in Krull was published on **December 23, 1998** as WO 98/58079. As such, the descriptions of Chee and Krull have been available to those of skill in the art for nearly **7 years**. If Chee and Krull could teach all of the elements of the instant claims, and if Chee and Krull could be properly be combined with motivation to combine (as argued by the Examiner), Applicants must ask why they are the first and only ones to develop their sequencing substrate and apparatus? Why, in 7 years, have no other skilled artisans been able to construct the claimed invention? In view of the Human Genome Project (1990-2003) which necessitated sequencing 3 billion base pairs, why have no others been able attain Applicants' superior technology? The failure of others to produce Applicants' invention is compelling proof that Chee and Krull cannot make obvious the instant claims.

As a final consideration, Applicants note that an earlier position held by the Office should not be set in concrete with any rebuttal evidence evaluated only on its "knockdown ability." *See In re Rinehart*, 531 F.2d 1048, 1052 (C.C.P.A. 1976); MPEP §2144.08. The Office is expected to consider the facts for rebuttal (i.e., objective evidence for nonobviousness) with a fresh eye, and restart analysis under §103. *See In re Piasecki*, 745 F.2d at 1472; *In re Rinehart*, 531 F.2d at 1052. Any finding must rest on evaluation of all the facts in evidence, uninfluenced by any earlier conclusion reached for the alleged *prima facie* case. *See Id.* For at least these

[12] Submitted with Applicants' Information Disclosure Statement on June 12, 2003.

reasons, as well as the reasons set forth in the Amendment and Response mailed October 14, 2005, the instant claims cannot be considered obvious over Chee and Krull.

Reconsideration is respectfully requested.

CONCLUSION

A favorable action on the merits is respectfully requested. If further discussion of this case is deemed helpful, the Examiner is encouraged to contact the undersigned at the telephone number provided below, and is assured of full cooperation in progressing the instant claims to allowance. While Applicants believe that no additional fees are required, the Commissioner is authorized to charge or credit the undersigned Deposit Account No. 50-0311, Reference No. 21465-501 CIP2, Customer No. 35437, for any additional fees needed.

Respectfully submitted,

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